# Attenuation of the Pressor Response to Laryngoscopy and Tracheal Intubation - A Comparative Study of Lignocaine, Fentanyl, and Esmolol

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**ABSTRACT**

**BACKGROUND**

Laryngoscopy and intubation of the trachea causes increases in pulse rate and blood pressure. This is due to sympathoadrenal discharge caused by epipharyngeal and parapharyngeal stimulation. Unfortunately, the complete answer to this seemingly simple co-occurrence of laryngoscopy and tracheal intubation remains elusive. We wanted to compare the effects of three drugs namely lignocaine, fentanyl, esmolol for obtunding the haemodynamic response to laryngoscopy and intubation.

**METHODS**

A total of 60 adult patients undergoing elective spinal surgical procedures were included in the study. The patients were randomised to receive pre-intubation bolus of fentanyl (2 mcg / Kg), esmolol (0.5 mg / Kg) and lignocaine (1.5 mg / Kg) 3, 2 and 1.5 minutes before intubation, respectively. We measured pulse rate, SBP, DBP, and MAP prior to intubation and then subsequently at 1, 2, 3, 5, and 10 minutes after intubation. Data was analysed with SPSS 19 software.

**RESULTS**

The pulse rate, blood pressure and the MAP were found to be effectively controlled in the fentanyl group. The increase in pulse rate in the lignocaine group was found to be highly significant at all points of time as compared to the pre-intubation rate ($p < 0.0001$). In the fentanyl group, we observed a fall in the pulse rate; however, this fall in pulse rate was not significant ($p > 0.05$). An increase in the pulse rate was observed in the Esmolol group. When compared to pre-intubation, this rise was found to be significant in the 1$^{st}$ to 5$^{th}$ minute, after which the change in rate in the 10$^{th}$ min was not significant when compared to the pre intubation rate.

**CONCLUSIONS**

Fentanyl, in a dose of 2 µgm / Kg I.V., was a safe and effective agent in controlling the increase in heart rate and blood pressure in response to laryngeal stimulation and airway instrumentation.

**KEYWORDS**

Attenuation of Pressor Response, Laryngoscopy, Tracheal Intubation, Haemodynamic Stress Response, Fentanyl, Esmolol, Lignocaine

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## BACKGROUND

King BD[1] et al in a pioneering article, titled 'Reflex circulation responses to direct laryngoscopy and endotracheal intubation performed during general anaesthesia' first described the undesirable hyperdynamic responses to laryngoscopy and endotracheal intubation. There has been a lot of research across the globe on the haemodynamic response to laryngoscopy and tracheal intubation in patients. This research is still ongoing and has attracted a lot of interest due to no definitive answer till now. These transient sympathoadrenal responses, usually of no consequence in the majority of patients, can cause arrhythmias, myocardial ischemia and left ventricular failure in patients with pre-existing CAD and rupture of cerebral aneurysm and increased intracranial pressure in patients with pre - existing cerebrovascular disease and Traumatic brain injury. Anaesthetists have tried various techniques to blunt these haemodynamic responses, from non-pharmacological methods viz smooth, swift laryngoscopy[2] and deeper planes of anaesthesia at the time of laryngoscopy to volatile anaesthetic agents, Lignocaine topically on the larynx or I.V.,[3] opioids, Dexmedetomidine[4] antihypertensives and vasodilators like sodium nitroprusside, nitroglycerine,[5] calcium channel blockers[6] and adrenergic blockers[7] etc. However, a disadvantage of all these techniques is that the effect outlasts the indication for which it is used. Esmolol, fentanyl and Lignocaine are some of the short – acting anaesthetic agents used to attenuate the haemodynamic responses and circumvent the disadvantage of any long - lasting effects.

Esmolol hydrochloride is an adrenergic (beta-1 selective) receptor - antagonist which has a rapid onset and extremely short duration of action. It does not show any significant sympathomimetic activity at clinical dosages used. The rapidly metabolism occurs by the action of RBC esterases which hydrolyse its ester bonds. It has a distribution half - life of close to 2 minutes and the elimination half - life is about 9 minutes. The corresponding free acid and methanol are the metabolic end products of which the acid metabolite's elimination half-life is about 3.7 hours and is excreted in the urine, it's clearance following the glomerular filtration rate. Being cardioselective, it causes decreased heart rate, prolongs the sinus node recovery time and the AV interval during normal sinus rhythm and even with Atrial pacing. Due to this property, it has been found not to affect the Asthma patients in various studies.

Lidocaine Hydrochloride is a local anaesthetic agent chemically designated as acetamide, 2- (diethylamino) – N - (2, 6 - dimethyl phenyl) - monohydrochloride and causes reversible interruption of the conduction of impulses in peripheral nerves and at these doses does not have any sympathetic activity. Its absorption is complete after parenteral injection, the rate of depending upon the site of administration and the addition of a vasoconstrictor agent, if any. The drug concentration affects the plasma binding of lidocaine and the bound fraction decreases with increase in its concentration. Lidocaine crosses the blood-brain and placental barriers, by passive diffusion. It is rapidly metabolised in the liver. Excretion of the metabolites and unchanged drug is by the renal route. The excretion of Lignocaine is about 90 % as various metabolites and 10 % as unchanged drug. IV bolus of Lignocaine has an elimination half - life of approximately 1.5 to 2.0 hours. While hepatic dysfunction prolongs the half - life by two - fold or more, Lidocaine excretion through the kidneys is not affected by Renal dysfunction but it does cause the accumulation of metabolites.

Fentanyl citrate, is N - (1 – Phenethyl – 4 - piperidyl) propionamide citrate (1 : 1), a pure opioid agonist, which acts on opioid mu - receptors located in the brain and spinal cord resulting in analgesia and sedation. As is evident, its site of action is the central nervous system (CNS). The other effects it produces are nausea, sedation, depression of Respiration, bradycardia, postural hypotension, pruritis, euphoria and confusion. It gets rapidly distributed to the brain, heart, lungs, kidneys and spleen after its absorption and is later slowly redistributed to muscles and fat. It is 80 – 85 % bound to the plasma proteins majorly to alpha – 1 - acid glycoprotein and albumin. Rest is bound to lipoproteins. It is metabolized to nor-fentanyl in the liver and the intestinal mucosa, by the 3A4 isoform of the enzyme cytochrome P450. N - Dealkylated and hydroxylated inactive metabolites are formed by biotransformation which are finally eliminated from the body mainly with urine. Less than 7 % of the dose administered is excreted unchanged in the urine while approximately 1 % of the drug is excreted unchanged in the faeces.

This study aimed to compare all three agents concerning the reduction in incidence and severity of cardiovascular/haemodynamic responses during laryngoscopy and tracheal intubation.

## METHODS

This was a randomised control trial to compare the effects of the three drugs conducted after due permission and ethical clearance from the institutional ethical committee of NIMS Medical College and Hospital, Jaipur, Rajasthan. Informed consent was taken from all patients considered for the study. 60 patients of American Society of Anesthesiologists (ASA) grade I and II aged 18 to 55 years who were scheduled to undergo elective spinal surgical procedures were included in the study. We excluded patients with known severe cardiovascular, respiratory, renal or hepatic dysfunction, those with a difficult airway and those with a history of use of any Alpha or Beta-2 agonist or Beta blocking drugs.

We calculated the total sample size assuming an alpha of 0.05, power of 80 % and effect size of 0.40 for three groups and five measurement in each group with minimum correlation of 0.25 and nonsphericity correction of 0.6. The calculated sample size came out to be 20 in each group, hence we randomly allocated 20 patients into each group. Block randomisation to one of the three groups was done by making five blocks of 12 subjects each. Randomisation was done within each block and equal number of treatment were ensured. Each block was kept in a serially number opaque envelope. The patients were administered the drugs in the

following doses

Lignocaine 1.5 mg / Kg IV, 1.5 minutes before laryngoscopy (Group 1),

Fentanyl 2 µgm / Kg IV, 3 minutes before laryngoscopy (Group 2) and

Esmolol 0.5 mg/ Kg IV, 2 minutes before laryngoscopy (Group 3).

All patients were premedicated with a similar protocol, for anxiolysis, with Midazolam 0.02 mg / Kg I.V. in the pre - operative room. In all the patients pre oxygenation was done for 3 minutes with 100% oxygen. Induction was done with Inj Propofol 1.5 - 2 mg / Kg I.V., till the loss of eyelash reflex. This was followed by the study drug (optimally timed from laryngoscopy as per the protocol). Relaxation was achieved with Inj Vecuronium 0.1 mg / Kg I.V. Smooth, swift and gentle Laryngoscopy with appropriately sized Macintosh blade was attempted after 3 min. The patients were intubated using an appropriately sized cuffed Endotracheal tube. Multiple attempts at insertion were avoided. Patients were subsequently maintained on 35 % nitrous oxide in oxygen. Neither any other intravenous or inhalational agent nor any surgical stimulus (catheterization or marking the level) was allowed to be administered to the patient during the following study period of 10 minutes. The parameters recorded for the study were, pulse rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP). Each reading was taken at the one - minute interval for the first five minutes after laryngoscopy and tracheal intubation and then at ten minutes finally. The ECG, EtCO2, NIBP, SpO2 and the E.C.G. were recorded throughout the study period. The Mean Arterial Pressure (MAP) was defined as a: {DAP + (SAP / 3) / 2}.

**Statistical Analysis**

Data is summarized and presented as mean with standard deviation and numbers or percentages where applicable. All the means were compared using one way ANOVA and Tukey's post hoc test. The analyses were performed using SPSS software package version 19 (SPSS Inc., Chicago, IL). We considered a value of $p < 0.05$ as significant.

## RESULTS

The baseline characteristics of the patients included in the three groups are shown in Table 1. The mean weight in all three groups was comparable (P = 0.99). There was no difference in the distribution of males and females in the three groups ($X^2$ (2, N = 60) = 1.0048, P = 0.605)

| Characteristics | Esmolol | Fentanyl | Lignocaine | P Value |
|---|---|---|---|---|
| Mean age in years (SD) | 39.60 (4.2) | 39.65 (5.1) | 39.5(3.2) | F = 0.0065, P = 0.99 |
| **Gender** | | | | |
| Male n (%) | 6 (30) | 7 (35) | 9 (45) | $X^2$ (2, N = 60) = 1.0048, P = 0.605 |
| Female n (%) | 14 (70) | 13 (65) | 11 (55) | |
| Weight in Kg (SD) | 65 (4.7) | 64 (5.1) | 62 (4.3) | F = 2.102 P = 0.131 |

***Table 1. Baseline Characteristics***

Table 2 depicts the change in pulse rate in the three groups. The increase in pulse rate in the lignocaine group was found to be highly significant at all points of time as compared to the pre intubation rate ($p < 0.0001$).In the fentanyl group, we observed a fall in the pulse rate; however, this fall in pulse rate was not significant ($p > 0.05$). An increase in the pulse rate was observed in the Esmolol group when compared to the pre intubation this rise was found to be significant in the 1st to 5th minute, after which the change in rate in the 10th min was not significant when compared to the pre intubation rate. When the pulse rates in the three groups were compared using an ANOVA test, we found the mean pulse rate to be significantly different from the 1st-minute post - intubation till the 5th min. The pulse rate in the fentanyl group was found to be significantly different lower than that in both the Lignocaine and the esmolol group from the 1st to the 5th minute. No difference between the three groups was found in the 10th minute. We did a Turkey test for post hoc analysis and found that at each time interval, the mean pulse rate of the fentanyl group was significantly different from that in the other two groups. However, the difference in the mean pulse rates in the Lignocaine and the esmolol group were not found to be significantly different.

| Time | Lignocaine Pulse Rate (SD) | Fentanyl Pulse Rate (SD) | Esmolol Pulse Rate (SD) | P Value |
|---|---|---|---|---|
| Pre-Intubation Post-Intubation | 89.6 (7.4) | 96.9 (13.6) | 90.6 (15.2) | F = 1.996, P = 0.142 |
| 1 min | 106.9 (8.8) | 90.7 (10.1) | 111.9 (9.6) | F = 27.13, P = 0.000 |
| 2 min | 106.4(9.3) | 89.6 (10.0) | 110.1 (10.1) | F = 24.82, P = 0.000 |
| 3 min | 105.9 (8.8) | 90.1 (11.5) | 99.1 (12.7) | F = 10.15, P = 0.0002 |
| 4 min | 102.0 (9.6) | 89.9 (11.5) | 96.7 (15.5) | F = 4.75, P = 0.0124 |
| 5 min | 100.7 (9.4) | 90.2 (11.2) | 96.7 (15.5) | F = 3.711, P = 0.035 |
| 10 min | 97.8 (8.5) | 96.9 (10.4) | 92.5 (15.1) | F = 1.18, P = 0.3412 |

***Table 2. Comparison of Pulse Rate at Different Time Intervals in the Three Groups***

The change in blood pressure during the period of anaesthesia is depicted in Figure 1. The systolic arterial pressure in the lignocaine group at all periods was higher than the baseline value. The difference from the baseline was significant in the 1st to 4th minute, and after that, it ceased to be significantly different. In the fentanyl group, a fall in the systolic blood pressure was noticed post-intubation; however, this fall was not found to be significant at any of the periods, when compared to the baseline value. The Esmolol group showed a sharp rise in blood pressure in the first minute and after that continued to be elevated until the 10th minute. The increase was found to be significant when compared to the baseline, till the 5th minute. Thereafter the difference in SBP was not found to be different in the 10th minute.

The diastolic blood pressure in the lignocaine group dropped from 81.4 to 80.6 mmHg in the 1st minute and stayed at that value till the 4th minute, after which it fell in the 5th minute, but again rose above the baseline level in the 10th minute. The change in the SBP from the baseline value was only found to be significant int eh 10th minute. In the fentanyl group, the SBP fell post-intubation, and the fall was maintained until the 10th minute. However, this differs from the baseline value was not found to be significant. In the

esmolol group, a significant increase in the diastolic BP was observed in the 3rd to 5th minutes.

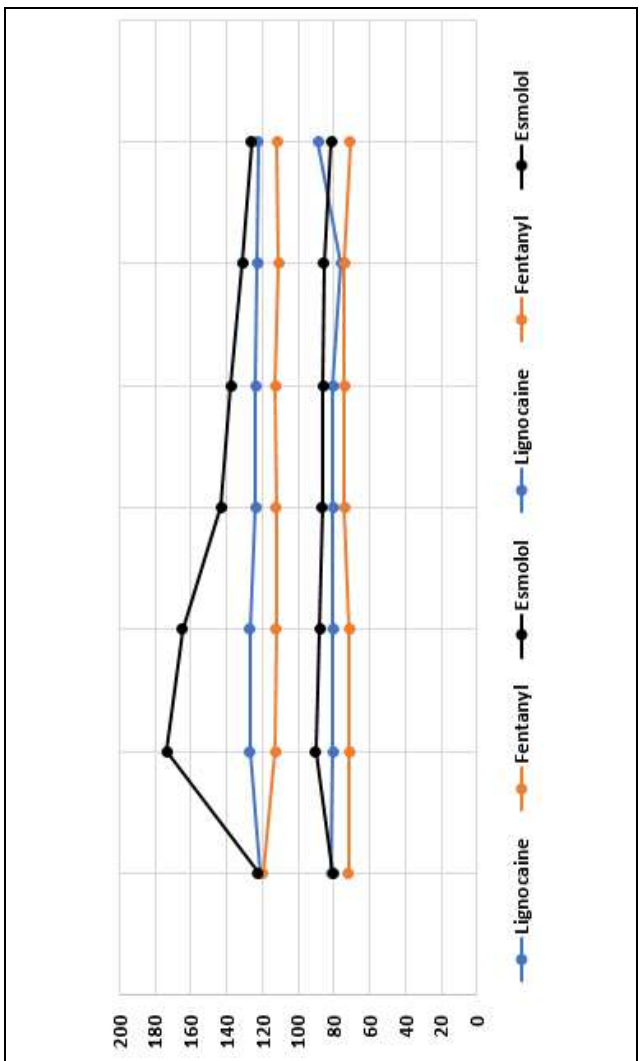


***Figure 1. Comparison of Systolic and Diastolic Blood Pressure at Different Time Intervals***

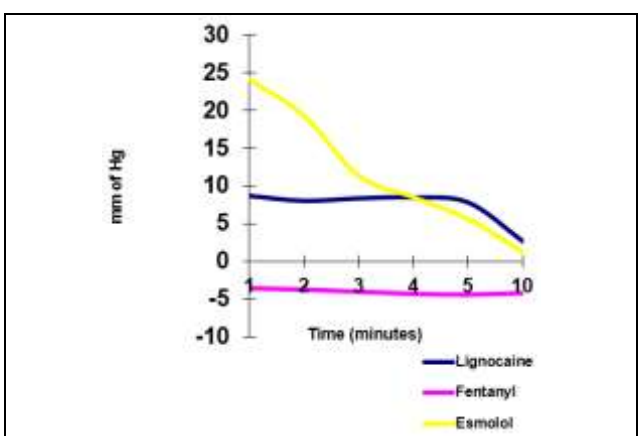


***Figure 2. Percentage Changes in MAP in the Three Groups***

Figure 2 shows the change in MAP in all three groups of patients. In the patients receiving Lignocaine, the postintubation MAP values were higher than the baseline at all times except the 10th minute; however, the change was found to be statistically significant ($p < 0.001$) in the first 5 minutes. In patients receiving fentanyl, the postintubation MAP was lower than the baseline at all times. The change was gauged to be statistically insignificant ($p > 0.05$). In the esmolol group, the postintubation MAP values were higher than the baseline at all times. The difference was found to be statistically significant ($p < 0.001$ in the first 3 mins and $p < 0.01$ in the 4th and 5th mins and $p < 0.05$ in the 10th minute).

## DISCUSSION

In our study, Lignocaine in the dose of 1.5 mg / Kg I.V., showed an unpredictable effect in the attenuation of the reflex circulatory response to laryngoscopy and tracheal intubation. The effect of Lignocaine was more defined on the blood pressure than the heart rate. We found Esmolol to be ineffective in controlling either the reflex increase in heart rate or blood pressure. Fentanyl in a dose of 2 µgm / Kg I.V. was effective in controlling the rise in heart rate and blood pressure in response to laryngeal stimulation and airway instrumentation. Fentanyl maintained lower heart rate and blood pressure despite laryngoscopy and intubation. Out of the three drugs, we found fentanyl to be useful for the attenuation of the pressor response to laryngoscopy and tracheal intubation. Maldeet al. also reported more effective attenuation of pressor response with fentanyl as compared to Lignocaine.[8] Several other authors have found fentanyl to be effective in controlling SBP, MAP and DBP.[9–11] In a recent randomised control trial which compared low dose Fentanyl with Lignocaine, the authors reported that though rise in heart rate was attenuated by both Lignocaine and fentanyl, fentanyl controlled heart rate more effectively. Lignocaine attenuated the increase in blood pressure with intubation, whereas fentanyl prevented it.[12] Gurulingappa et al. in 2012,[13] reported a similar finding, when comparing fentanyl and Lignocaine. They reported that fentanyl as compared to Lignocaine, provided a more reliable, consistent, and effective attenuation of increase in Heart rate. A recent clinical trial by Maziaret al. from Iran reported the apparent superiority of fentanyl over both dexmedetomidine and lidocaine in attenuation of the haemodynamic response of laryngoscopy and intubation.[14]

Some other authors have found esmolol to be superior to fentanyl in attenuating the haemodynamic responses associated with laryngoscopy and intubation. Gupta et al. compared esmolol with fentanyl and reported excellent results with esmolol.[15] In a prospective, randomised, a double-blind study carried out in Turkey which compared Esmolol, Lidocaine and Fentanyl, the authors found esmolol to be beneficial in the prevention of tachycardia and RPP.[16] An earlier study by Feng CK et al[17] also reported that while esmolol blunted the increase in both HR and SBP, Fentanyl (3 micrograms / Kg) was effective in preventing hypertension but failed to prevent tachycardia and lignocaine (2 mg / Kg) was ineffective in controlling both haemodynamic responses during the period of laryngoscopy and endotracheal intubation.

## CONCLUSIONS

Both Lignocaine and esmolol, in the doses used, were ineffective in controlling either the tachycardia or hypertension. Fentanyl (2 µgm / Kg I.V.), was found to be a safe and effective agent for controlling tachycardia and hypertension in response to laryngeal stimulation and airway instrumentation. Fentanyl decreased the heart rate and blood pressure to a lower level and maintained it at these lower values, even in the face of laryngoscopy and intubation.

**Limitations**

A limitation of our study is that none of our patients had any comorbidity, and hence the results of this study may not be applicable in situations where patients have comorbid conditions.

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